

A REVIEW OF PHARMACOGENETIC STUDIES CONCERNING GENETICS AND TREATMENT RESPONSE IN PARKINSON'S DISEASE

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder that progressively deteriorates the nervous system. Its causes are multifaceted, involving environmental influences, genetic predispositions, and epigenetic modifications. The main and inciting symptoms of PD are a combination of motor (bradykinesia, rest tremor and rigidity) and non-motor (hallucinations, compulsive behaviours and sleep disorders) symptoms. The existing treatments are mainly composed of a combination of medications that focus on treating the symptoms of the disease by replacing the lost dopamine without identifying the cause of the disease. Although beneficial, these therapies display a concerning amount of heterogeneity in drug response. Pharmacogenetics, a part of pharmacogenomics, helps to highlight the genetic factors that contribute to such heterogeneity in drug response. In the treatment of patients with PD, pharmacogenetic studies are particularly important given the variability of results, primarily concerning levodopa and dopaminergic therapies. This review covers the genetic mutation related to PD genes such as LRRK2, SNCA, and PARK2, which will be taken into account concerning their effects on disease progression and drug response. Genetic polymorphisms can significantly modulate the efficacy and adverse effects of drugs in patients with PD, influencing drug metabolism, transport, and receptor binding, among others, and involve genes such as CYP2D6 and COMT. This would be achieved through the application of pharmacogenetic insights that allow for tailored therapy approaches, optimize dosages, reduce adverse effects, and ensure better patient outcomes. Personalized medicine in PD could potentially enable improvement in treatment strategies based on an individual's genetic profile and thereby enhance management for this complex disease.

Keywords: Pharmacogenetics, Parkinson's Disease, Genetic Variability, Drug Response, Neurodegenerative Disorders, Personalized Medicine.

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, affecting more than six million individuals globally.

Being a chronic neurodegenerative disorder, Parkinson's disease mainly affects the flexibility due to continuous outflow of dopaminergic neurons from the substantia nigra part of the brain. Though its non-engine symptoms include mental

deterioration, sleep problems, and autonomic dysfunction, it is best described by engine symptoms such as tremors, bradykinesia, stiffness, and postural instability [1]. The production of Lewy bodies, which hinder standard cell movement, is the result of a development of misfolded alpha-synuclein proteins in the cerebrum, which is important for the complicated pathophysiology of Parkinson's disease [2]. Albeit the precise beginning of PD is still obscure, a blend of environmental and genetic factors is believed to be responsible. As per epidemiological information, PD is the second most predominant neurodegenerative affliction after Alzheimer's disease, influencing 1% to 2% of those older than 65. Men are almost certain to have it more than women, and the rate rises with age. The degenerative idea of PD and the absence of viable therapies overburden medical services systems around the world. Major advancements have been made in understanding the neuropathology and progression of Parkinson's disease through the nervous system, as well as in uncovering the molecular and neurophysiological mechanisms behind the condition and its symptoms [3]. Most notably, highly effective treatments now exist, with dopamine replacement therapy (l-DOPA) at the core, along with notable improvements and innovations such as deep brain stimulation. These breakthroughs have established Parkinson's disease as the prime example of a neurodegenerative disorder that can be managed effectively, enabling long-term control of symptoms and improved quality of life for many years post-diagnosis. However, despite these treatments, Parkinson's remains a progressive disease that eventually leads to severe disability, particularly due to increasing treatment-resistant motor issues and non-motor symptoms. Therefore, slowing disease progression and delaying disability are key challenges for both current and future research. An area with significant potential is the development of strategies to identify individuals at risk and recognize early signs that appear before the classic motor symptoms [4]. Despite growing research efforts on pharmacogenetic variability in Parkinson's disease, results are still scattered and not systematically integrated into clinical practice. There are many studies that show a relationship between genetic variations and treatment response, but the strength, replicability, and practical value of such results are unclear. This review aims to critically assess the existing pharmacogenetic evidence in Parkinson's disease, explore the existing and novel gene-drug associations, and examine the strength of the existing evidence. By concentrating on therapeutic response instead of the broader disease genetics, this review seeks to fill an important gap between scientific discovery and the development of personalized therapies for PD [5].

1.1. Epidemiology

The World Health Organization has recognized PD as a global concern, highlighting its rapid growth in middle- and low-SDI nations as well. According to the Global Burden of Disease, injuries, and Risk Factors study (GBD), PD has shown the fastest recent rise in prevalence, disability, and mortality among neurological disorders [5]. This shift underscores the increasing global impact of the disease [6]. Prevalence increases markedly with age, rising from approximately 0.3% in the general population to over 3% in individuals older than 80 years. Incidence estimates range between 5 and 35 cases per 100,000 person-years, with higher rates observed in older populations and in men



Figure 1: Symptoms of Parkinson's disease

compared to women [5]. Although environmental exposures such as pesticides and traumatic brain injury have been associated with increased risk, heritability estimates suggest that genetic factors contribute approximately 22-40% to disease susceptibility. This gene-environment interaction framework is particularly relevant in understanding variability not only in disease risk but also in treatment response [7].

1.2. Pathogenesis

Parkinson's disease is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta and subsequent dopamine depletion in the striatum. The pathological hallmark of the disease is the accumulation of misfolded α -synuclein within Lewy bodies. From a pharmacogenetic perspective, several molecular mechanisms are particularly relevant. Dopamine homeostasis is regulated by enzymes such as catechol-O-methyltransferase (COMT) and monoamine oxidase B (MAO-B), both of which influence synaptic dopamine availability and modify the clinical response to levodopa and MAO-B inhibitors [8]. In addition, cytochrome P450 enzymes, particularly CYP2D6, contribute to the metabolism of certain dopaminergic agents and may affect systemic drug exposure. Genetic differences in dopamine receptor genes (such as

DRD2 and *DRD3*) affect the sensitivity of dopamine receptors and their downstream signalling pathways, thus affecting pharmacodynamic responses and the risk of adverse reactions to drugs, including dyskinesia, hallucinations, and impulse control disorders. Moreover, mutations in genes such as *LRRK2* and *GBA1* are now being identified not only as contributing factors to the pathogenesis of PD but also as potential therapeutic targets. Therefore, although neuronal degeneration is the underlying cause of the symptoms of PD, the genetic component plays a crucial role in determining the variability of pharmacodynamic responses. Other factors, such as mitochondrial dysfunction, oxidative stress, neuroinflammation, and lysosomal dysfunction, play a major role in the pathogenesis of PD [9].

1.3. Clinical Features Relevant to Pharmacogenetics

Parkinson's disease presents with both motor and non-motor symptoms. The major motor symptoms include bradykinesia, resting tremor, rigidity, and postural instability, which are mainly due to striatal dopamine deficiency. Non-motor symptoms like depression, dementia, autonomic dysfunction, and sleep disorders also add considerably to the burden of the disease [10]. In pharmacogenetics, the issue of variability in the occurrence of complications related to treatment assumes special significance. Chronic levodopa treatment can cause motor fluctuations and levodopa-induced dyskinesia, while dopamine agonists cause impulse control disorders, hallucinations, and psychiatric problems in susceptible subjects [6]. These adverse effects are not equally likely in all patients and are now recognized to be affected by genetic polymorphisms related to dopamine metabolism, receptor expression, and drug clearance. Thus, the search for genetic predictors of treatment response and adverse effects is an important step towards tailoring treatment in Parkinson's disease [4].

1.3.1. Symptoms

The symptoms of Parkinson's disease might manifest differently in each individual. The first warning signals may be imperceptible. Symptoms often begin on one side and progress to the other. Usually, one side has more severe symptoms compared to the other. There are several shared symptoms between Parkinson's disease and other diseases [8].

Parkinson's disease affects movement and daily activities in several ways. Tremors often begin in the hands, especially at rest, and may lessen during movement. People may also experience slowed

actions, making routine tasks harder, along with muscle stiffness, reduced facial expressions, and difficulty with balance or posture [11]. Automatic movements like blinking or arm swinging may decrease, and speech can become softer or monotone. Handwriting often becomes small and cramped. In addition to these motor symptoms, many individuals also face non-motor issues such as depression, anxiety, constipation, sleep problems, reduced sense of smell, memory difficulties, and persistent fatigue [12].

1.4. Pharmacogenetics and Its Importance

A branch of pharmacogenomics called pharmacogenetics studies how a person's genetic composition affects how they react to medications. Pharmacogenetics is especially relevant to Parkinson's disease since genetic variables account for a major portion of the illness's heterogeneity in treatment response [13]. The way that PD treatments, such as levodopa and dopamine agonists, compensate for dopamine depletion in the brain varies greatly from patient to patient in terms of both effectiveness and adverse effects. The above differences are caused mostly by genetic polymorphisms, especially in genes encoding transporters, receptors, and enzymes involved in drug metabolism. It is through such a comprehension of the pharmacogenetic aspects of PD that not only prearranged treatment plans can be prepared, but also previews of adverse responses to certain medications, maximization of dose, and, consequently, improvement of the quality of life in patients with Parkinson's disease. Also, in pharmacogenetics for PD, optimization of efficacy coupled with minimal adverse effects is the ultimate aim in moving toward personalized medicine, where therapy is tailored to each patient's genetic profile [14].

1.5. Distinction Between Pharmacogenetics and Pharmacogenomics

Pharmacogenetics and pharmacogenomics are fields of study that are closely related but differ in their conceptual framework. The term pharmacogenetics has traditionally been used to describe the investigation of the role of differences in a single gene on an individual's susceptibility to a particular drug [14]. Early studies in pharmacogenetics in Parkinson's disease were largely candidate gene-based, involving genes such as *COMT*, *CYP2D6*, *DRD2*, and *MAO-B* [15]. In contrast, pharmacogenomics involves a more comprehensive and genome-wide approach that considers the joint effects of multiple genes and regulatory elements on drug response. This includes genome-wide association studies, polygenic risk modeling,

transcriptome analysis, and systems biology approaches. In the context of Parkinson's disease, pharmacogenomic approaches are being increasingly explored to define molecular subtypes, assign patients for personalized therapies (such as *LRRK2*-targeted therapies), and develop predictive models of treatment response [16]. Although the current literature in Parkinson's disease is largely based on pharmacogenetic candidate gene approaches, the area is gradually moving towards more comprehensive pharmacogenomic models. This review article will cover both areas, focusing on established gene-drug interactions and emerging genome-wide approaches.

2. Genetic factors influencing parkinson's disease

Parkinson's disease can be considered a genetic disorder in a narrow sense, as some patients carry rare, well-defined causal variants that lead to familial forms of the disease. In a broader sense, many individuals with Parkinson's have a polygenic risk, influenced by multiple common genetic risk variants. Heritability estimates from twin studies and statistical genetic methods range between 22% and 40%, suggesting that both genetic and environmental factors contribute significantly to the development of Parkinson's disease [17].

2.1. Genetic Mutations Associated with PD

Genetic abnormalities are responsible for a significant proportion of the cases of Parkinson's disease, with hereditary features both in familial and in sporadic cases [18]. A few of the most studied PD genes are *LRRK2*, *SNCA*, *PARK2*, *PINK1*, *VPS35* and *DJ-1*. Out of these, *SNCA*, *VPS35* and *LRRK2* are autosomal dominant genes, and the remaining three are autosomal recessive genes; all of these genes are properly validated [19]. Moreover, single rare and common variants in the *GBA1* gene or Gaucher disease-causing gene, responsible for Gaucher disease and encoding glucocerebrosidase, have been associated with Parkinson's disease. While these variants are linked to the condition, they generally do not segregate in autosomal dominant families [18]. Autosomal dominant *LRRK2* gene mutations are believed to contribute the most towards the etiology of familial as well as sporadic PD. The most prevalent mutation in *LRRK2* gene in North African, European and Jewish kindreds is observed to be Gly2019Ser, in Chinese kindreds it is Asn1437Asp and in Japanese kindreds it is Ile2020Thr. In addition, the Gly2385Arg variant in *LRRK2* increases the risk of Parkinson's disease in Chinese and Korean populations, with an odds ratio around 2.4. *LRRK2* is also associated with the development of conditions such as Crohn's disease,

mycobacterial infections, and leprosy [19]. It is possible that the *LRRK2* locus has pleiotropic effects, influencing both resistance and susceptibility to inflammatory, infectious diseases, as well as contributing to neurodegeneration.

A protein known as alpha-synuclein, encoded by the *SNCA* gene, linked to hereditary as well as sporadic forms of Parkinson's disease, associates with the formation of Lewy bodies. Further evidence also implicates the disease with alterations of this gene. On the contrary, autosomal recessive mutations of the *PARK2* gene are associated with early-onset Parkinson's disease. Aside from α -synuclein, mitochondrial dysfunction is the major component of Parkinson's disease pathophysiology and can be caused by mutations in the *PINK1* and *DJ-1* genes. Collectively, these genetic changes have enhanced our understanding of molecular events that define Parkinson's disease and suggest therapeutic avenues [20].

2.2. Impact of Genetics on Disease Progression

The vulnerability of a person to acquiring Parkinson's disease, along with its onset, progression, and severity, is largely influenced by genetic factors. For example, late-onset PD has been linked to mutations within the *LRRK2* gene, while mutations in *PARK2*, *PINK1*, *DJ-1*, and *PARK2* are often associated with early-onset PD [21]. Some of these genetic abnormalities might accelerate this disease progression, putting one in a category that may be more likely have such a predisposition towards non-motor symptoms like depression or dementia and rapid decline of the motor functions. Conversely, some genetic factors may be associated with milder phenotypes or better progress pace. Early cognitive impairment and motor dysfunction are the symptoms of more severe forms of PD related to the *SNCA* gene, particularly in its amplification. Better prognosis and, perhaps, alternative treatment options for individuals with distinctive genetic profiles may be achieved through a better understanding of the roles played by these genetic variations in the development of the disease [22].

2.3. Pharmacogenetic Variability

This accounts for most pharmacogenetic variability in the treatment of Parkinson's disease patients. Variations in the genes for *CYP* and other enzymes may affect the metabolism of drugs used for treatment of PD in a way that could significantly alter their efficacy or otherwise increase the risk for adverse effects. For instance, it is established that the ability of the dopaminergic drugs like levodopa to be metabolized depends on the genetic variation in the gene *CYP2D6*, thereby affecting its plasma levels as well as consequently the response to treatment [23]. Furthermore, genetic variation in other enzymes like *COMT*, which breaks down dopamine, establishes the period for which levodopa

and other antiparkinsonian drugs, which sustain dopaminergic activity, are active in the system. The effectiveness and side effect profile of dopaminergic drugs may be impacted through dopamine receptor polymorphisms (DRD2, DRD3); and thereby also the way different people respond to these drugs. Such pharmacogenetic parameters indicate that, with the aims to maximize the responsiveness to drug in PD treatment, customized treatment plans according to the genetic profile of the patient would be required [24].

3. Pharmacogenetic influence on treatment response

3.1. Levodopa and Dopaminergic Therapies

Pharmacogenetic factors take the major role in the efficacy and side effects of levodopa therapy. There are variability effects on both side effects and therapeutic effects of levodopa via drug levels in the brain. Such variability results from polymorphisms of the COMT gene coding for the metabolic enzyme of this medication. For instance, the COMT Val158Met polymorphism influences the duration of levodopa's action as it is either metabolized faster or slower [25]. Variations in the DRD2 gene encoding the D2 dopamine receptor also impact the brain's reactivity to dopaminergic stimulation and might influence the effectiveness and timing of untoward effects associated with its use, such as dyskinesias. It becomes easier to understand these genetic variations so that better therapeutic interventions can be targeted, including adjusting the dose of levodopa or using COMT inhibitors to prolong its action [26].

3.2. Other Pharmacological Treatments

Other pharmacological treatments for PD other than levodopa are dopamine agonists (including pramipexole, ropinirole), COMT inhibitors (such as entacapone), and MAO-B inhibitors (such as selegiline, rasagiline). The efficacy of these drugs may be modulated by genetic factors. For instance, polymorphisms in the MAO-B gene could modify the expression and thus the activity of the enzyme and the potency of MAO-B inhibitors, which do not allow dopamine to be metabolized [27]. As was described previously, polymorphisms in the COMT gene alter responsiveness to COMT inhibitors on the prolongation of levodopa's half-life. The response of patients to dopamine agonists could also be influenced by polymorphisms in the genes encoding dopamine receptors, DRD2, and DRD3; some polymorphisms increase susceptibility to side effects such as delusional scenarios or impairments

of impulse control. These pharmacogenetic insights will then become imperative when the patients react adversely to conventional drugs or show very poor side effects [24].

3.3. Personalized Treatment Approaches

The introduction of pharmacogenetics in treating Parkinson's disease will be the opening up of a possibility towards tailoring treatment plans and adjusting medications in accordance with a patient's genetic profile [28]. This is possible due to the identification of genetic variants that affect the metabolism of medications, responsiveness to medications, and potential toxicity, making it possible for medical professionals to tailor treatment regimens in a manner that would optimize the efficacy and minimize adverse effects. For example, people carrying certain polymorphisms in COMT or CYP2D6 will benefit from dose adjustment or treatment with enzyme inhibitors to maximize the effect of their drugs. Pharmacogenetic testing can also help identify people most likely to experience motor adverse effects or other adverse effects from dopaminergic treatments early on or help select alternative treatments instead [29]. To enhance the clinical relevance of this review, only pharmacogenetic studies directly examining gene-drug interactions in Parkinson's disease are summarized in Table 1. Studies unrelated to PD were excluded to maintain focus on disease-specific therapeutic variability. The table highlights the current strength of evidence and the degree of clinical applicability for each gene-drug interaction.

Table 1: Key Pharmacogenetic Studies in Parkinson's Disease.

Gene	Variant	Drug/Therapy	Clinical Outcome	Evidence Summary	Clinical Relevance
COMT	Val158Met (rs4680)	Levodopa	Duration of response; dyskinesia risk	Multiple cohort studies; moderate but inconsistent findings	Not recommended for routine testing
CYP2D6	*3, *4, *5 alleles	Dopamine agonists	Altered drug metabolism	Limited observational evidence	Investigational

			and adverse effects	ence; small sample sizes	
<i>DR D2</i>	Taq1A (rs1800497)	Dopamine agonists	Impulse control disorders	Emerging associations; requires replication	Potential risk stratification
<i>DR D3</i>	Ser9Gly (rs6280)	Dopamine agonists	Behavioral side effects	Mixed results; moderate evidence	Not yet clinically actionable
<i>MAO-B</i>	rs1799836	MAO-B inhibitors	Variability in treatment response	Limited and population-specific findings	Insufficient for clinical use
<i>LR RK 2</i>	G2019S	Targeted therapies (clinical trials)	Precision therapeutic targeting	Strong genetic association; therapeutic relevance emerging	High future potential

3.4. Comparative Influence of Genetic Variants on Treatment Outcomes

Although several genetic variants have been associated with treatment response variability in Parkinson's disease, the relative clinical significance of these variants is not uniform. Among the candidate genes, the *COMT* Val158Met variant is the most widely studied in association with levodopa treatment response and dyskinesia risk, although it has shown only moderate and inconsistent replication. Conversely, the role of *CYP2D6* polymorphisms in dopaminergic drug metabolism in PD seems to be of relatively smaller clinical significance compared with their well-established role in psychiatric pharmacogenetics. The role of dopamine receptor variants (*DRD2*, *DRD3*) is more strongly associated with behavioral adverse reactions, such as impulse control disorders, rather than motor function. Novel precision medicine strategies based on *LRRK2* mutations mark a new era in the translation of modest-effect pharmacogenetic variants into genotype-specific

therapies with potentially greater clinical significance [30].

4. Current research and clinical applications

4.1. Recent Pharmacogenetic Studies

Pharmacogenetic research in Parkinson's disease has contributed greatly to our understanding of the influence of genetic variation on pharmacological response [31]. Of late, particular attention has been paid to genes implicated in the metabolism of dopamine, which are relevant to the pathophysiology of PD. For example, changes in the level of dopamine in the brain have been linked to the polymorphism in the gene for *COMT* (catechol-O-methyltransferase), and this affects the response of a patient to levodopa, the main treatment for PD [32]. Polymorphisms in genes such as *DRD2* (dopamine receptor D2) and *MAO-B* (monoamine oxidase B) have been identified as contributing factors in the variable drug effectiveness of the agonist class of dopamine and MAO-B inhibitors. The metabolism of numerous drugs varies from person to person due to the association of certain genetic variations with drug metabolism, more specifically for the *CYP2D6* enzyme [33]. More recent studies began to include genes related to the function of mitochondria and neuroinflammation, which have more recently been acknowledged to contribute to PD pathophysiology and treatment outcomes. In particular, the field of targeted therapies for Parkinson's disease has been actualized through research on the leucine-rich repeat kinase 2 (*LRRK2*) gene, commonly mutated in familial Parkinson's disease. Taken together, these pieces of evidence highlight the growing complexity of pharmacogenetics in PD, where therapy can be fine-tuned to an individual patient's genetic profile, so that treatments are more maximally and personally applied to the particular needs of that patient [34].

4.2. Clinical Trials and Studies

Pharmacogenetics is thus becoming more significant because the therapeutic strategies for this disease are enhanced through the incorporation of the individual genetic profile [35]. This approach requires pharmacogenetic markers to have been included in clinical trials on Parkinson's disease to classify patients on how they might react to specific medicines. For instance, variations in the *COMT* and *ADORA2A* genes across different variants were being investigated in levodopa-centred studies and related to issues of motor impairment and drug-induced dyskinesias [32]. They are directed toward reducing toxic side effects and finding ideal doses

by means of genetic susceptibility to specific adverse effects or poor responses to treatment. Similarly, clinical studies of dopamine agonists and MAO-B inhibitors are evaluating the first hypothesis that a genetic variation in DRD2, MAO-B, and other genes determines the outcome of the treatment. Clinical studies gave more attention to the *LRRK2* gene and treatment in mutation carriers 2 [36]. Precisely, such developments of precision medicine have further encouraged research endeavours involved with examinations of gene treatments and innovative pharmaceutical approaches to be customized for certain genetic subtypes of PD. Although their large-scale adoption is just beginning, such pharmacogenetically guided studies represent a step toward individualized therapy in PD. With more pharmacogenetic information available, clinical studies should be able to successfully identify patients who would benefit from a particular type of drug, which would have better clinical outcomes [37].

4.3. Challenges in Translating Pharmacogenetics to Clinical Practice

Incorporation of pharmacogenetics into routine clinical practice for PD presents a number of challenges, although promising studies. Chief among them is the complexity of Parkinson's disease's genetic etiology. PD is a very heterogeneous condition, with individuals showing an enormous variability in their genetic makeup and disease course. Although some gene variants have been associated with treatment responses, many genetic factors are still poorly characterized [38]. Major obstacles also include the cost and accessibility of genetic testing. In many countries, most health systems have restricted their use in routine practice because it is not easily accessible, or rather, it is expensive. Additionally, many clinicians sometimes lack the requisite training to understand the results of the tests, which will most likely result in uneven uptake in practice. Pharmacogenetic testing can be illustrative of a patient's greater genetic risk factors, which has raised privacy and consent issues. It also raised ethical and regulatory issues [39]. Another challenge is that the number of large, long-term studies that show the unique therapeutic benefit of pharmacogenetic testing in Parkinson's disease is scarce. While promising preliminary data exist, much more substantial information is required for physicians and policymakers to begin using the tests extensively. Finally, pharmacogenetic information entering clinical decision-making will require sequential and iterative updates of clinical guidelines. Much promise exists for improving patient care, but probably

pharmacogenetic discoveries will be limited to routine PD therapy until these challenges are overcome [40].

5. Conclusion

Pharmacogenetic research is of extreme importance in advancing our knowledge regarding Parkinson's disease and treatment. Thus, transferring pharmacogenetic findings into clinical practice may allow more patient-tailored treatments. Genetic variants influencing drug metabolism, dopaminergic signalling, and receptor pharmacodynamics contribute to differences in therapeutic efficacy and susceptibility to adverse drug reactions. Genetic variants associated with drug metabolism, drug effectiveness, and adverse drug reactions can be recognized and used to adjust therapies accordingly in improving outcomes for the patient. This method decreases the possibility of complications and even improves the activity of drugs that are currently in practice, such as levodopa and dopamine agonists, in order to decrease the quality-of-life-related issues of a patient with PD. Pharmacogenetics is in its nascent stages, but it can change personalised treatment for PD and make safer alternatives possible for the betterment. However, although several candidate-gene associations have been identified, the overall clinical impact of most single genetic variants remains modest, and findings across studies are sometimes inconsistent. At present, routine pharmacogenetic testing in Parkinson's disease is not widely implemented due to limited large-scale prospective validation studies and the absence of standardized clinical guidelines. Future research integrating genome-wide approaches, multi-omics data, and genotype-guided clinical trials will be essential to translate pharmacogenetic discoveries into practical precision medicine strategies for Parkinson's disease.

6. References

1. Su D, Cui Y, He C, Yin P, Bai R, Zhu J, Feng T. Projections for prevalence of Parkinson's disease and its driving factors in 195 countries and territories to 2050: modelling study of Global Burden of Disease Study 2021. *BMJ*. 2025;388:e080474. doi: 10.1136/bmj-2024-080474.
2. Calabresi P, Di Lazzaro G, Marino G, Campanelli F, Ghiglieri V. Advances in understanding the function of alpha-synuclein: implications for Parkinson's disease. *Brain*. 2023;146(9):3587–3597. doi: 10.1093/brain/awad167.
3. Subramanian I, Mathur S, Oosterbaan A, Flanagan R, Keener AM, Moro E. Unmet needs of women living with Parkinson's disease: gaps and controversies. *Movement Disorders*. 2022;37(3):444–455. doi: 10.1002/mds.28894.
4. Iarkov A, Barreto GE, Grizzell JA, Echeverria V. Strategies for the treatment of Parkinson's disease: beyond dopamine. *Frontiers in Aging Neuroscience*. 2020;12:4. doi: 10.3389/fnagi.2020.00004.
5. Chaparro-Solano HM, Paz MR, Anis S, Hockings JK, Kundrick A, Piccinin CC, Mata IF. Critical evaluation of the current landscape of pharmacogenomics in Parkinson's disease—what is missing? A systematic review. *Parkinsonism & Related Disorders*. 2025;130:107206. doi: 10.1016/j.parkreldis.2025.107206.
6. Ma Z, Zou S, Liu R, Li S, Li Z. Socioeconomic development index (SDI) gradients and high BMI-driven pan-cancer burden: a global burden of disease study on mortality, disability, and health inequities (2015–2021). *BMC Public Health*. 2025;25(1):3295. doi: 10.1186/s12889-025-22663-9.
7. Lipsky RH, Witkin JM, Shafique H, Smith JL, Cerne R, Marini AM. Traumatic brain injury: molecular biomarkers, genetics, secondary consequences, and medical management. *Frontiers in Neuroscience*. 2024;18:1446076. doi: 10.3389/fnins.2024.1446076.
8. Ramesh S, Arachchige ASPM. Depletion of dopamine in Parkinson's disease and relevant therapeutic options: a review of the literature. *AIMS Neuroscience*. 2023;10(3):200.
9. Zhao M, Ma J, Li M, Zhang Y, Jiang B, Zhao X, Qin S. Cytochrome P450 enzymes and drug metabolism in humans. *International Journal of Molecular Sciences*. 2021;22(23):12808. doi: 10.3390/ijms222312808.
10. Pagonabarraga J, Tinazzi M, Caccia C, Jost WH. The role of glutamatergic neurotransmission in the motor and non-motor symptoms in Parkinson's disease: clinical cases and a review of the literature. *Journal of Clinical Neuroscience*. 2021;90:178–183. doi: 10.1016/j.jocn.2021.05.008.
11. Micaglio E, Locati ET, Monasky MM, Romani F, Heilbron F, Pappone C. Role of pharmacogenetics in adverse drug reactions: an update towards personalized medicine. *Frontiers in Pharmacology*. 2021;12:651720. doi: 10.3389/fphar.2021.651720.
12. Nour M, Senturk U, Polat K. Diagnosis and classification of Parkinson's disease using ensemble learning and 1D-PDCovNN. *Computers in Biology and Medicine*. 2023;161:107031. doi: 10.1016/j.combiomed.2023.107031.
13. Qahwaji R, Ashankyty I, Sannan NS, Hazzazi MS, Basabrain AA, Mobashir M. Pharmacogenomics: a genetic approach to drug development and therapy. *Pharmaceuticals*. 2024;17(7):940. doi: 10.3390/ph17070940.
14. Riederer P, Strobel S, Nagatsu T, Watanabe H, Chen X, Löschmann PA, Monoranu CM. Levodopa treatment: impacts and mechanisms throughout Parkinson's disease progression. *Journal of Neural Transmission*. 2025;132(6):743–779. doi: 10.1007/s00702-025-02710-3.
15. Dhiman A, Mehan S, Khan Z, Tiwari A, Das Gupta G, Narula AS. Hereditary patterns and genetic associations in obsessive-compulsive disorder (OCD): neuropsychiatric insights, genetic influences, and treatment perspectives. *Current Gene Therapy*. 2024.
16. Qahwaji R, Ashankyty I, Sannan NS, Hazzazi MS, Basabrain AA, Mobashir M. Pharmacogenomics: a genetic approach to drug development and therapy. *Pharmaceuticals*. 2024;17(7):940. doi: 10.3390/ph17070940.
17. Outeiro TF, Alcalay RN, Antonini A, Attens J, Bonifati V, Cardoso F, Ferreira JJ. Defining the riddle in order to solve it: there is more than one "Parkinson's disease". *Movement Disorders*. 2023;38(7):1127–1142. doi: 10.1002/mds.29281.
18. Cherian A, Divya KP. Genetics of Parkinson's disease. *Acta Neurologica*

- Belgica. 2020;120(6):1307–1315. doi: 10.1007/s13760-020-01379-8.
19. Over L, Brüggemann N, Lohmann K. Therapies for genetic forms of Parkinson's disease: systematic literature review. *Journal of Neuromuscular Diseases*. 2021;8(3):341–356. doi: 10.3233/JND-210651.
 20. Srinivasan E, Chandrasekhar G, Chandrasekar P, Anbarasu K, Vickram AS, Karunakaran R, Srikumar PS. Alpha-synuclein aggregation in Parkinson's disease. *Frontiers in Medicine*. 2021;8:736978. doi: 10.3389/fmed.2021.736978.
 21. Morris HR, Spillantini MG, Sue CM, Williams-Gray CH. The pathogenesis of Parkinson's disease. *The Lancet*. 2024;403(10423):293–304. doi: 10.1016/S0140-6736(23)01478-2.
 22. Radad K, Moldzio R, Krewenka C, Kranner B, Rausch WD. Pathophysiology of non-motor signs in Parkinson's disease: some recent updating with brief presentation. *Exploration of Neuroprotective Therapy*. 2023;3(1):24–46. doi: 10.37349/ent.2023.00087.
 23. Liu JS, Chen Y, Shi DD, Zhang BR, Pu JL. Pharmacogenomics—a new frontier for individualized treatment of Parkinson's disease. *Current Neuropharmacology*. 2023;21(3):536–546. doi: 10.2174/1570159X20666221121143526.
 24. Fabbri M, Ferreira JJ, Rascol O. COMT inhibitors in the management of Parkinson's disease. *CNS Drugs*. 2022;36(3):261–282. doi: 10.1007/s40263-022-00871-4.
 25. Liu JS, Chen Y, Shi DD, Zhang BR, Pu JL. Pharmacogenomics—a new frontier for individualized treatment of Parkinson's disease. *Current Neuropharmacology*. 2023;21(3):536–546. doi: 10.2174/1570159X20666221121143526.
 26. Magistrelli L, Ferrari M, Furgiuele A, Milner AV, Contaldi E, Comi C, Marino F. Polymorphisms of dopamine receptor genes and Parkinson's disease: clinical relevance and future perspectives. *International Journal of Molecular Sciences*. 2021;22(7):3781. doi: 10.3390/ijms22073781.
 27. Schneider A, Sari AT, Alhaddad H, Sari Y. Overview of therapeutic drugs and methods for the treatment of Parkinson's disease. *CNS & Neurological Disorders – Drug Targets*. 2020;19(3):195–206. doi: 10.2174/1871527319666200127110040.
 28. Liu JS, Chen Y, Shi DD, Zhang BR, Pu JL. Pharmacogenomics—a new frontier for individualized treatment of Parkinson's disease. *Current Neuropharmacology*. 2023;21(3):536–546. doi: 10.2174/1570159X20666221121143526.
 29. Langmia IM, Just KS, Yamoune S, Brockmöller J, Masimirembwa C, Stingl JC. CYP2B6 functional variability in drug metabolism and exposure across populations—implication for drug safety, dosing, and individualized therapy. *Frontiers in Genetics*. 2021;12:692234. doi: 10.3389/fgene.2021.692234.
 30. Leonard H, Blauwendraat C, Krohn L, Faghri F, Iwaki H, Ferguson G, Gan-Or Z. Genetic variability and potential effects on clinical trial outcomes: perspectives in Parkinson's disease. *Journal of Medical Genetics*. 2020;57(5):331–338. doi: 10.1136/jmedgenet-2019-106521.
 31. Leonard H, Blauwendraat C, Krohn L, Faghri F, Iwaki H, Ferguson G, Gan-Or Z. Genetic variability and potential effects on clinical trial outcomes: perspectives in Parkinson's disease. *Journal of Medical Genetics*. 2020;57(5):331–338. doi: 10.1136/jmedgenet-2019-106521.
 32. Latif S, Jahangeer M, Razia DM, Ashiq M, Ghaffar A, Akram M, Ansari MA. Dopamine in Parkinson's disease. *Clinica Chimica Acta*. 2021;522:114–126. doi: 10.1016/j.cca.2021.07.002.
 33. Zapała B, Stefura T, Piwowar M, Czekalska S, Zawada M, Hadasik M, Rudzińska-Bar M. The role of single nucleotide polymorphisms of monoamine oxidase B, dopamine D2 receptor, and DOPA decarboxylase receptors among patients treated for Parkinson's disease. *Journal of Molecular Neuroscience*. 2022;72(4):812–819. doi: 10.1007/s12031-022-02037-8.
 34. Picca A, Guerra F, Calvani R, Romano R, Coelho-Júnior HJ, Bucci C, Marzetti E. Mitochondrial dysfunction, protein misfolding and neuroinflammation in Parkinson's disease: roads to biomarker discovery. *Biomolecules*. 2021;11(10):1508. doi: 10.3390/biom11101508.
 35. Pirmohamed M. Pharmacogenomics: current status and future perspectives. *Nature Reviews Genetics*. 2023;24(6):350–362. doi: 10.1038/s41576-023-00579-5.
 36. Merghany RM, El-Sawi SA, Naser AFA, Ezzat SM, Moustafa SF, Meselhy MR. A comprehensive review of natural compounds and their structure–activity relationship in Parkinson's disease: exploring potential mechanisms. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2025;398(3):2229–2258. doi: 10.1007/s00210-024-03249-9.

37. Wang RC, Wang Z. Precision medicine: disease subtyping and tailored treatment. *Cancers*. 2023;15(15):3837. doi: 10.3390/cancers15153837.
38. Tenchov R, Sasso JM, Zhou QA. Evolving landscape of Parkinson's disease research: challenges and perspectives. *ACS Omega*. 2025;10(2):1864–1892. doi: 10.1021/acsomega.4c06340.
39. Filip R, Gheorghita Puscaselu R, Anchidin-Norocel L, Dimian M, Savage WK. Global challenges to public health care systems during the COVID-19 pandemic: a review of pandemic measures and problems. *Journal of Personalized Medicine*. 2022;12(8):1295. doi: 10.3390/jpm12081295.
40. Stocchi F, Bravi D, Emmi A, Antonini A. Parkinson disease therapy: current strategies and future research priorities. *Nature Reviews Neurology*. 2024;20(12):695–707. doi: 10.1038/s41582-024-01089-9.